Milvexian Does Not Prolong the QTc Interval: A Thorough QT Study in Healthy Subjects

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BACKGROUND/OBJECTIVE

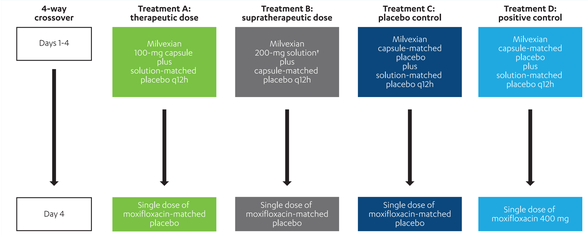
- Milvexian is an oral, small-molecule, selective, active-site inhibitor of activated clotting factor XI.[1] Ongoing phase 3 studies will evaluate milvexian for the prevention of thrombotic events following ischemic stroke (25 mg twice daily, NCT05702034) or acute coronary syndrome (25 mg twice daily, NCT05754957) and in atrial fibrillation (100 mg twice daily, NCT05757869)
- The present study evaluated the effect of milvexian on cardiac repolarization and other electrophysiologic parameters in healthy participants, an important aspect of cardiovascular safety

METHODS

Participants and Study Design

- This was a randomized, double-blind, double-dummy, placebo- and positive-controlled, multiple-dose, 4-treatment, 4-period, crossover, phase 1 study (**Figure 1**)
- All participants were randomly assigned to 1 of 4 intervention sequence groups and received 1 of 4 treatments in each treatment period (**Figure 1**)
  - The intervention sequence groups were ADBC, BACD, CBDA, and DCAB (n = 15 participants per sequence)

Figure 1. A schematic overview of the study design.*



q12h, every 12 hours.
*Each treatment period was separated by a washout period of 5 to 28 days between Day 5 of the previous treatment period and Day 1 of the next treatment period.
†The solution consisted of 80% (w/w) polyethylene glycol 400 and 20% (w/w) polysorbate 80.

- Eligible participants included males and females 18 to 55 years of age who had a body mass index of 18 to 30 kg/m^2, had a total body weight of >50 kg, and were nonsmokers who were generally in good health
- Study intervention was administered orally with 220 mL of water approximately q12h on Days 1 through 4. Participants fasted overnight prior to each morning administration. On Days 1 and 4, the fast continued for an additional 4 hours after study drug administration

Study Assessments

- 12-lead Holter electrocardiograms (ECGs) were obtained from predose to up to 24 hours postdose on Days 1 and 4
- ECGs were recorded using a digital 12-lead dual-lead ECG recorder. Lead II was the primary lead. Three 10-second ECGs were extracted within 4 minutes
- ECGs were assessed using a high-resolution, semi-automatic, on-screen caliper method. Cardiologists were blinded to treatment group, treatment period, time point, and participant identifiers. A single cardiologist analyzed all ECGs from an assigned participant
- Corrected QT intervals were derived using the following methods: Fridericia (QTcF), Bazett (QTcB), and study-specific power (QTcP; regression modeling of the baseline QT/RR data pooled from all participants in the study)
- Plasma pharmacokinetic samples were collected at the same predetermined times as ECGs
- The safety and tolerability of milvexian were assessed by changes from baseline in physical examinations, vital sign measurements, and 12-lead safety ECGs, as well as by safety laboratory tests and documentation of adverse events (AEs)

Modeling of ΔΔQTcF and Plasma Milvexian Concentrations

- The relationship between placebo-corrected change from baseline in QTcF (ΔΔQTcF) and plasma milvexian concentrations was evaluated using a prespecified linear mixed-effects model (implemented in *R*):
  - Equation 1: $\Delta\Delta QTcF \sim (\beta_0 + \eta_{i0}) + (\beta_1 + \eta_{i1}) \times \text{milvexian concentration} + \beta_2 \times QTcF0 + \epsilon$
    - β_0 and β_1 are the intercept and the slope of the linear concentration-effect relationship, respectively
    - Baseline QTcF in each study period (QTcF0) was included as a continuous covariate in the model, taken as the difference from population mean baseline (ie, centered baseline), together with its associated fixed-effect β_2
    - The random effects η_{i0} and η_{i1} quantified the interindividual variability on the intercept and the slope, respectively
    - The residual variability, ϵ, represented the random noise

CONCLUSIONS

- **Overall, administration of milvexian was safe and well tolerated**
- **Milvexian did not have a clinically relevant effect on QTc intervals and other ECG parameters at therapeutic and supratherapeutic doses**
- **Milvexian is not expected to prolong the QTc interval at exposures that will be achieved in patients who are enrolled in the three ongoing phase 3 studies of the Librexia program**
- **The results support a standard approach of collecting on-therapy ECGs from patients in the ongoing phase 3 studies in accordance with current practices**
- **Ongoing phase 3 studies have implemented standard-of-care ECG assessments that improved study feasibility by significantly reducing the burden for study participants and decreasing the resource utilization associated with intense ECG monitoring**

Reference

1. Wong P, et al. *J Thromb Haemost*. 2022;20(2):399-408.

Acknowledgments

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Disclosures

PZ, **JP**, **AD**, **ST**, **ANP**, **JJPR**, and **NG** are employees of Janssen Research & Development, LLC, a Johnson & Johnson Company, and may be shareholders of Johnson & Johnson. **AM** is an employee and shareholder of Kura Oncology, Inc., and was an employee of Janssen Research & Development, LLC, a Johnson & Johnson Company, at the time of the study. **AA-H** and **SM** are employees and shareholders of Bristol Myers Squibb.

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RESULTS

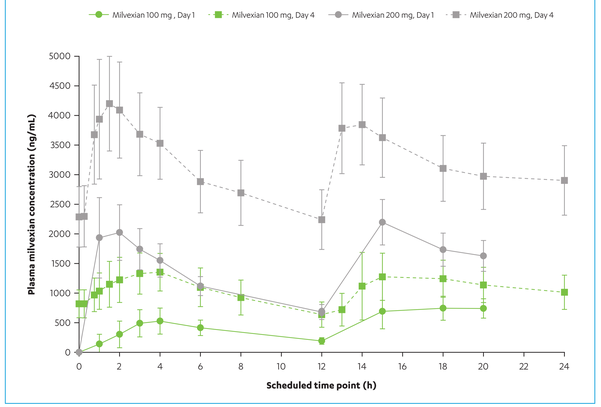
Participants and Dataset

- 66 participants were enrolled in the study:
  - Participants had a mean (standard deviation [SD]) age of 33.5 (11.0) years and mean (SD) body mass index of 25.2 (2.77) kg/m^2; 53% were male
  - 45 participants completed all 4 periods
- The analysis dataset included 4630 time-matched plasma milvexian concentration and ECG data points

Plasma Milvexian Concentrations

- A dose-dependent increase in plasma milvexian concentrations was observed
  - Concentrations were substantially higher on Day 4 relative to Day 1 (**Figure 2**)

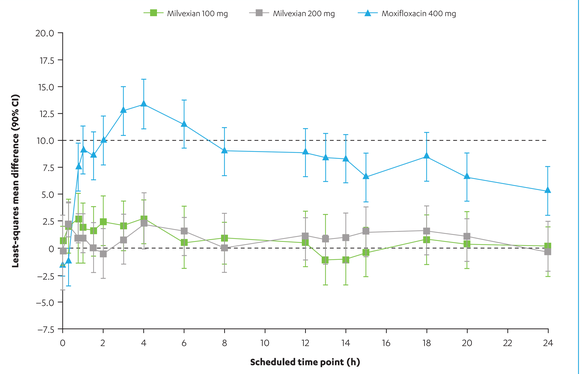
Figure 2. Mean (SD) plasma milvexian concentration-time profiles after oral administration of milvexian 100 mg (capsule) or 200 mg (solution) q12h for 4 days.



QTc Intervals

- The upper limit of the 2-sided 90% confidence interval (CI) of the least-squares mean ΔΔQTcF was <10 msec at all time points on Days 1 and 4 (**Figure 3**)
  - Similar results were obtained for the Bazett and study-specific power correction methods (not shown)
- No participant had a QTc >480 msec at any time; there were no changes from baseline in QTcF or QTcP >60 msec, and 1 (1.7%) participant had a change from baseline of QTcB >60 msec during the study (ie, following moxifloxacin)
- No differences by sex were observed
- QT assay sensitivity for detecting drug-induced QTc prolongation was demonstrated by moxifloxacin (**Figure 3**)

Figure 3. Least-squares mean difference (90% CI) in change from baseline QTcF intervals between milvexian 100 mg or 200 mg administered q12h or a single dose of moxifloxacin 400 mg and placebo.



Data from Day 4 are shown.

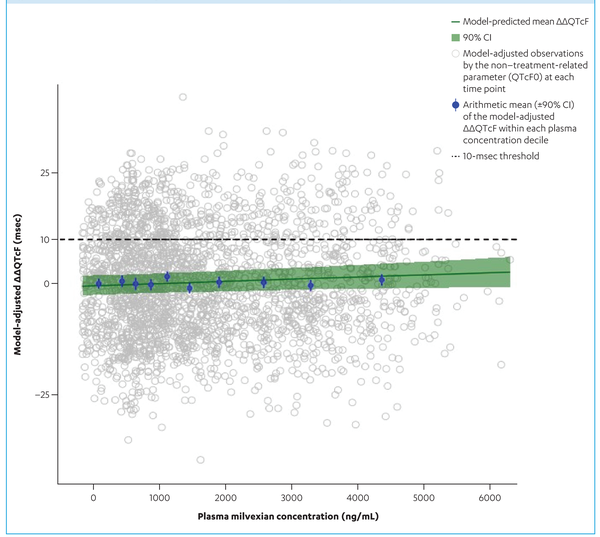
Modeling of ΔΔQTcF and Plasma Milvexian Concentrations

- The following assumptions that were required for using the prespecified linear mixed-effects model that assessed the relationship between ΔΔQTcF and plasma milvexian concentrations were met:
  - Milvexian did not have an effect on heart rate
  - Use of the Fridericia correction was confirmed by QTc interval versus RR interval
  - Hysteresis was not apparent
  - ΔΔQTcF and plasma milvexian concentration did not indicate a nonlinear relationship
- Model-predicted ΔΔQTcF and observed model-adjusted ΔΔQTcF versus plasma milvexian concentrations were well described (**Table 1** and **Figure 4**)
  - The slope estimate was positive but not significantly different than 0
  - The model-predicted means and corresponding 90% CIs for ΔΔQTcF at the geometric mean of maximum plasma milvexian concentration on Day 4 following q12h administration of a 100-mg capsule (1496 ng/mL) and 200-mg solution (4436 ng/mL) were <4.66 msec

Table 1. Final Parameter Estimates From the Concentration-QTc Analysis (Linear Mixed-effects Model) to Evaluate the Relationship Between ΔΔQTcF and Plasma Milvexian Concentration

Parameter	Unit	Estimate	Standard error
β_0 (intercept)	msec	−0.495	1.35
β_1 (slope)	msec/(µg/mL)	0.502	0.286
QTcF0 (centered baseline QTcF)	msec	−0.433	0.0464
η_{i0} (interindividual variability on the intercept)	msec	9.62	–
η_{i1} (interindividual variability on the slope)	msec/(µg/mL)	1.84	–
ϵ (residual variability)	msec	7.07	–

Figure 4. Model-predicted ΔΔQTcF and observed model-adjusted ΔΔQTcF versus plasma milvexian concentrations.



Safety

- No consistent or clinically relevant changes over time were observed in heart rate, RR interval, PR interval, or QRS width and no T-wave, U-wave, or other morphologic findings were reported
- No ECG abnormalities were reported as treatment-emergent AEs (TEAEs); treatment-emergent changes from baseline in ECG parameters were not considered significant
- No deaths or other serious AEs were reported
- No severe TEAEs were reported. The majority of TEAEs were mild (in 53 [80.3%] participants)
- The most frequently reported nonbleeding TEAEs (≥10%) following milvexian 100 mg, milvexian 200 mg, and placebo were headache (11 [20.0%], 15 [27.3%], and 15 [26.3%] participants, respectively), diarrhea (7 [12.7%], 29 [52.7%], and 3 [5.3%]), nausea (4 [7.3%], 7 [12.7%], and 4 [7.0%]), and abdominal pain (3 [5.5%], 9 [16.4%], and 3 [5.3%]). The higher incidence of diarrhea following milvexian 200 mg was attributed to the presence of polyethylene glycol 400 in the oral solution
- Most bleeding TEAEs were mild (in 21 [31.8%] participants). The most frequently reported bleeding TEAE (≥5.0%) was hematochezia in 3 (5.5%) participants following milvexian 200 mg; it was not reported in any participants after milvexian 100 mg, moxifloxacin, or placebo